

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/EP2004/014102	International filing date (day/month/year) 10.12.2004	Priority date (day/month/year) 16.12.2003	
International Patent Classification (IPC) or both national classification and IPC C07C213/08, C07C217/74			
Applicant KRKA, TOVARNA ZDRAVIL, D.D. NOVO MESTO			

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Zervas, B Telephone No. +31 70 340-3667
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/EP2004/014102

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2004/014102**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
- claims Nos. 10-26

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the whole application or for said claims Nos. 10-26
- the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form has not been furnished

does not comply with the standard

the computer readable form has not been furnished

does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/014102

Box No. IV Lack of unity of invention

1. In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
 - paid additional fees.
 - paid additional fees under protest.
 - not paid additional fees.
2. This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3
 - complied with
 - not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
 - all parts.
 - the parts relating to claims Nos. 1-9

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/014102

Re Item IV.

The separate inventions are:

1. claims 1-9:

A process for the preparation of venlafaxine which comprises converting a venlafaxine precursor in the presence of a salt of formic acid

2. claims 10-20:

A process for preparing venlafaxine hydrochloride of form I comprising the crystallization of venlafaxine hydrochloride of form I in an organic solvent which contains isopropyl acetate and/or cyclohexane

3. claims 21-26:

A process for the preparation of venlafaxine hydrochloride of form I comprising the reaction of venlafaxine with aqueous HCl in an organic solvent

The three inventions mentioned above are not so linked as to form a single inventive concept (Rule 13.1 PCT) for the following reason:

In view of the prior art documents D1 (WO 0246140) and D2 (J.Med.Chem. 33 (10), 2899 - 2905 (1990) the problem underlying the first invention can be defined as providing a further process for the preparation venlafaxine. To solve this problem, the applicant provides the process according to claims 1 - 9. Said process is characterized in that a venlafaxine precursor is converted in the presence of a formic acid salt.

In view of the document D1 the problem underlying the second invention can be defined as providing an alternative process for the preparation of venlafaxine hydrochloride of form I. To solve this problem the Applicant provides the process of claims 10 - 20 which is characterized in that venlafaxine hydrochloride of form I is crystallized from an organic solvent which contains isopropyl acetate and/or cyclohexane.

In view of the document D1 the problem underlying the third invention can be defined as providing an alternative process for the preparation of venlafaxine hydrochloride of form I.

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International application No.

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To solve this problem the Applicant provides the process of claims 21 - 26, which is characterized in that venlafaxine is reacted with aqueous HCl in an organic solvent.

The invention 1 attempts to solve a different problem than the inventions 2 and 3 and is characterized by different technical features. The only technical feature linking the invention 1 on one hand and the inventions 2 and 3 on the other hand is the compound venlafaxine. However, venlafaxine is a known compound and can therefore not be regarded as a special technical feature linking the invention 1 and the inventions 2 and 3.

The inventions 2 and 3 attempt to solve the same problem, namely the preparation of venlafaxine hydrochloride of form I. However, the processes of the inventions 2 and 3 are characterized by different technical features. The only common technical feature they have is the venlafaxine hydrochloride of form I which is prepared. Since the document D1 discloses already venlafaxine hydrochloride of form I it cannot be regarded as a special technical feature linking the inventions 2 and 3.

Re Item V.

Reference is made to the following document:

D1 : WO 02/45658 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; DOL) 13 June 2002 (2002-06-13)

1. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 9 is not new in the sense of Article 33(2) PCT. Document D1 (see D1, example 2) discloses already the preparation of venlafaxine from a venlafaxine precursor in the presence of the Na-salt of formic acid, which is prepared in situ. The subject-matter of claims 1 to 9 is therefore not novel in view of D1.

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No

PCT/EP2004/014102

2. Inventive Step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 9 does not involve an inventive step in the sense of Article 33(3) PCT.

Since the subject-matter of claims 1 - 9 is not novel it cannot be regarded as inventive either.

3. Industrial Applicability

The process of claims 1 - 9 can be industrially applied in the preparation of venlafaxine.

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